CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Elsevier - Publisher Connector

Cell Metabolism
Previews

miR-200 De-FOGs Insulin Signaling

Aurelio A. Teleman[1,*]
[1]German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany
*Correspondence: a.teleman@dkfz.de
DOI 10.1016/j.cmet.2009.12.004

Insulin signaling is a key regulator of metabolism and tissue growth in animals. Recent work in *Cell* (Hyun et al., 2009) defines two conserved components of the insulin pathway: a microRNA and the protein USH/FOG2.

The insulin/insulin-like growth factor (IGF)-signaling pathway regulates crucial aspects of organismal biology, including carbohydrate metabolism, lipid metabolism, tissue growth, and longevity (Grewal, 2009; Kitamura et al., 2003). As the "Chief Financial Officer" of a cell, insulin/IGF signaling gauges the environment for the availability of resources and decides whether to be sparing or aggressive with the use of these resources. It thereby regulates the balance between storage and breakdown of carbohydrates and lipids, as well as the degree to which cells grow, which is an energetically expensive process. As a consequence, altered insulin/IGF signaling is associated with a number of diseases. Reduced insulin signaling erroneously tells an organism to conserve energy in the form of glycogen and fat, contributing toward diabetes and obesity. Elevated insulin signaling spurs cell growth, contributing to cancer development (Bjornsti and Houghton, 2004).

Based on the importance of the insulin/IGF pathway and on isolation of insulin one century ago, one might expect that by now we would have a clear understanding of how insulin signaling works, and that this is all "textbook biology." In fact, this is far from true. Indeed, 40-odd components required for insulin signaling have been identified and characterized. These components interact to form a complex machine that senses the insulin signal, processes it, and regulates cellular physiology. Studying such a complex machine entails identifying and understanding each of the parts, then understanding how the parts work together as a whole, at the "system" level. One century after the discovery of insulin, we are still at step one: discovering the parts. A recent paper in *Cell* from V. Narry Kim's lab (Hyun et al., 2009) makes a significant contribution to this effort by describing not just one but two novel components of the insulin pathway (Figure 1).

Flies mutant for the microRNA (miRNA) *mir-8* exhibit malformed limbs and increased neuronal apoptosis (Karres et al., 2007). Hyun and colleagues noted that these flies are also small in size. Since insulin signaling regulates animal size, they measured activation of the insulin pathway in these flies and found that it was reduced. Hyun et al. then observed that miR-8 is strongly expressed in the fly fat body, which regulates *Drosophila* size. Insulin signaling in the fat body promotes insulin signaling and growth in other tissues of the animal via an unknown mechanism (Géminard et al., 2009). Consistent with this, Hyun et al. find that miR-8 expression in the fat body regulates the level of insulin signaling in this tissue, consequently affecting the size of the entire animal.

But what is the molecular mechanism underlying miR-8 function? miRNAs are small, regulatory RNAs that bind the 3′ UTRs of target mRNAs through base-pairing and inhibit mRNA translation by recruiting the RISC protein complex (Bartel, 2009). Since the miRNA/mRNA interaction can function even with imperfect base-pairing, computational algorithms have had difficulty identifying in vivo mRNA targets of specific miRNAs. To confront this problem, Hyun et al. started with the premise that important interactions between miR-8 and its targets should be evolutionarily conserved. The human homologs of miR-8 are the members of the miR-200 family. Therefore, Hyun et al. compared the predicted miR-8 targets in the fly with the predicted miR-200 targets in humans and identified the homologous gene pairs present in both lists. Cell-culture validation of the predictions left them with seven bona fide miR-8 targets. By testing whether knockdown of each of these seven genes in *mir-8* mutant flies could rescue their small body phenotype, they identified the gene *u-shaped* (*FOG2* in humans) as the miR-8 target relevant for regulating animal size.

Finally, Kim and colleagues studied how USH/FOG2 regulates insulin signaling. Upon binding insulin, the insulin receptor becomes activated and phosphorylates insulin receptor substrate-1 (IRS-1) (Figure 1). This causes recruitment and activation of the lipid kinase PI3K, composed of a catalytic subunit, p110, and a regulatory subunit, p85α. Hyun et al. found that FOG2 binds p85α, thereby inhibiting formation of the IRS-1/p85α/p110 complex and, consequently, PI3K activation. Expression of miR-200 causes FOG2 protein levels to drop, allowing insulin signaling to take place.

In sum, Hyun and colleagues have identified two novel, conserved components of the insulin-signaling pathway: miR-8/miR-200 and USH/FOG2. This study is interesting for a number of reasons: (1) It illustrates how a combination of in silico predictions and wet-lab experiments exploiting evolutionary conservation can successfully identify miRNA/mRNA interactions of biological significance. (2) It highlights that one miRNA can have multiple biological effects, each one mediated via a different target mRNA. Whereas here USH is identified as the miR-8 target regulating animal size, prior work had identified atrophin as the miR-8 target regulating apoptosis in the brain (Karres et al., 2007). Hyun et al. identify an additional six genes that are targeted by miR-8/miR-200, indicating likely additional functions for miR-8. (3) By identifying new insulin-signaling components, it opens the possibility of more complex regulation of the pathway. How are expression of *mir-8*/*mir-200* and *ush*/*FOG2* regulated at the transcriptional level? The interaction of FOG2 with PI3K at the

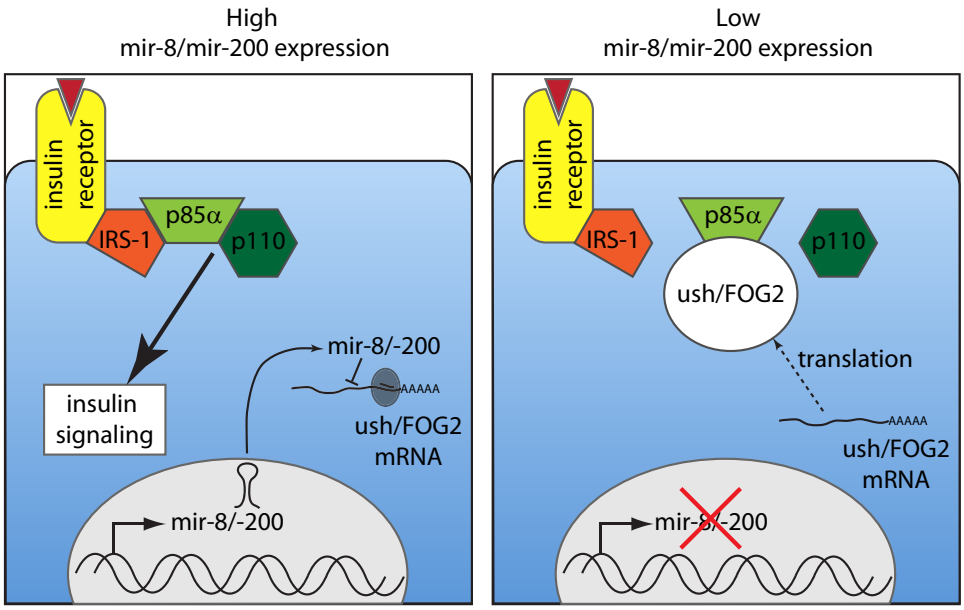

Figure 1. Regulation of Insulin Signaling by miR-8/200 and USH/FOG2
Expression of *mir-8* (in *Drosophila*) or *mir-200* (in humans) represses the translation of *ush* (*Drosophila*)/*FOG2* (human). As a consequence, the insulin receptor substrate-1 (IRS-1) is free to recruit the two subunits of phosphoinositide-3 kinase (PI3K), p85α and p110, to the insulin receptor. These then become activated, and signaling downstream of these components ensues. In the absence of *mir-8*/*mir-200* expression, USH/FOG2 protein is produced, and it binds p85α. Formation of the IRS-1/p85α/p110 complex is attenuated, as is signaling downstream of this complex.

cell membrane is somewhat surprising, because prior work demonstrated FOG2 to be a nuclear transcription factor. Is the shuttling of FOG2 between cytoplasm and nucleus regulated? (4) Since insulin signaling is medically relevant, this study suggests the possible involvement of *mir-8*/*mir-200* and *ush*/*FOG2* in cancer and metabolic disease should be evaluated.

The insulin signaling pathway as we currently know it consists mainly of positively acting factors, specifically a relay of kinases that phosphorylate and activate each other. However, as a key homeostatic regulator, the insulin pathway needs to be both activated and inactivated. Four negatively acting components were previously known to help keep activation of the pathway under control: the insulin-binding proteins, PTEN, Tsc1/2, and PP2A. This report adds a fifth: USH/FOG2. More are likely to come, suggesting it may take a while until we are done discovering all the components of insulin signaling.

REFERENCES

Bartel, D.P. (2009). Cell *136*, 215–233.

Bjornsti, M.A., and Houghton, P.J. (2004). Nat. Rev. Cancer *4*, 335–348.

Géminard, C., Rulifson, E.J., and Léopold, P. (2009). Cell Metab. *10*, 199–207.

Grewal, S.S. (2009). Int. J. Biochem. Cell Biol. *41*, 1006–1010.

Hyun, S., Lee, J.H., Jin, H., Nam, J.W., Namkoong, B., Lee, G., Chung, J., and Kim, V.N. (2009). Cell *139*, 1096–1108.

Karres, J.S., Hilgers, V., Carrera, I., Treisman, J., and Cohen, S.M. (2007). Cell *131*, 136–145.

Kitamura, T., Kahn, C.R., and Accili, D. (2003). Annu. Rev. Physiol. *65*, 313–332.